

Varenicline – a new pharmacotherapy for smoking cessation in primary care practice

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Abstract

Background: Cigarette smoking causes significant morbidity and mortality and is a major public health concern worldwide. Primary care doctors are in a unique position that enables them to promote smoking cessation, as smokers are more aware of their health at the time of their clinic visit. It is thus important to offer effective treatment to help smokers stop smoking.

Methods: A search of PubMed was done up to 16 December 2009, using the keywords “varenicline” alone, “varenicline” and “family medicine”, and “varenicline” and “primary care”. The search produced 426 articles on varenicline. The articles that were chosen were case reports, meta-analyses, review articles and clinical trials published in English.

Results: A new drug called varenicline has recently been introduced to assist smoking cessation. It is an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist. Varenicline has a unique action that relieves the cravings and withdrawal symptoms that occur during smoking abstinence, while blocking the receptor and preventing any reward from additional smoking. It has been shown to be efficacious for smoking cessation in normal smokers; however, its safety in smokers with mental health problems needs to be elucidated.

Conclusion: The currently available data support the effectiveness of varenicline to treat nicotine dependence, but caution is needed in smokers with mental health problems. Thus, primary care doctors have a new pharmacological option to offer smokers who wish to stop smoking.

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Introduction

Cigarette smoking is the single most important modifiable risk factor for cardiovascular disease. It also causes respiratory diseases, cerebrovascular diseases and cancer. Globally there are 1.3 billion smokers, and the majority of these are from developing countries.¹ The prevalence of smoking is 23% in the USA, 67% in China and 75% in Yemen. The present trend of smoking seen worldwide is also observed in Africa. The Medical Research Council (MRC) estimates that 8% of South African deaths are due to smoking, and the World Health Organization (WHO) has reported that smoking causes five million deaths per year. If the present trend continues, it is projected that, by the year 2025, up to 10 million smokers will die annually.² There is, therefore, an urgent need to identify an effective treatment to help smokers stop smoking.

Up to 70% of smokers visit a primary care doctor each year.³ Smokers have also been reported to be more aware of their health during these clinic visits. A primary care doctor thus has an important role, as the clinic visit provides an opportunity to offer smoking cessation interventions for smokers. Primary care doctors are also in a unique position as agents for smoking cessation because of their unique, personal doctor-patient relationship and their provision of comprehensive care. Primary care clinics are also more easily accessible to patients needing close supervision and support. It has been shown that brief advice offered by primary care doctors increases the rates of smoking cessation, but the addition of pharmacotherapy further enhances cessation outcomes.³

In recent years, much work has been published regarding what is effective in smoking cessation.⁴ The combined

use of pharmacotherapy and behavioural modification has consistently produced long-term smoking abstinence. A variety of pharmacological options are available to help smokers stop smoking. These options include nicotine-based medications, such as nicotine replacement therapy, and non-nicotine-based medications, such as bupropion, clonidine and nortriptyline.⁵ A new pharmacological agent called varenicline has recently been approved as a pharmacological agent for smoking cessation.⁵ Varenicline has been reported to have unique properties that help smokers refrain from smoking again.⁶

Why do smokers need to stop smoking?

The benefits of stopping smoking are well documented. By stopping smoking, a smoker gains short-term and long-term health benefits, reduces morbidity and mortality, and reverses disease progression associated with smoking.⁷ The risk of dying from heart disease is 70% greater in people who smoked compared to people who did not. Compared to a non-smoker, a cigarette smoker has an increased risk of hospitalisation due to heart failure and heart attack. However, people who quit smoking have been shown to have less risk of death due to heart disease. For instance, quitting smoking at the age of 35 increases life expectancy by 6.9 to 8.5 years for men and 6.1 to 7.7 years for women.⁸ Quitting smoking also reduces the risk of death for patients with left-heart failure and those who have undergone heart bypass surgery.

Lung function starts to improve within three months of quitting and ex-smokers experience decreased coughing, sinus congestion, fatigue and shortness of breath.⁹ The risk of coronary heart disease is reduced by 50% among ex-smokers one year after quitting and, by five years, the risk of stroke returns to the level of people who have never smoked. By 10 years after quitting, the risk of lung cancer reduces to 30 to 50% of those who continue to smoke and, by 15 years, the risk of cardiovascular heart disease becomes similar to those who have never smoked.^{7,9,10} Thus, smoking cessation increases life expectancy regardless of age at quitting, although the effect is better when quitting at an earlier age, in those who smoked fewer cigarettes and in those who smoked for fewer years.⁹ For example, stopping smoking at the age of 30 was shown to avoid smoking-related mortality, whereas stopping smoking at the age of 50 reduces the risk of death from smoking by half.¹¹

Source of data

A search of the literature up to 16 December 2009 was conducted using PubMed, with keywords “varenicline”

alone, “varenicline” and “family medicine”, and “varenicline” and “primary care”. The search produced a total of 426 articles on varenicline. The articles chosen were narrowed to those published in English and limited to studies done on human subjects. Case reports, meta-analyses, review articles and clinical trials evaluating the safety, efficacy and adverse effects of varenicline were included.^{6,12-21}

Nicotine dependence

Nicotine is responsible for the highly addictive nature of cigarette smoking. Stopping smoking is difficult because of nicotine dependence. Nicotine dependence is characterised by loss of control and compulsive drug-seeking behaviour. When inhaled, the nicotine in cigarette smoke is absorbed by the pulmonary alveoli, passes into the blood and enters the brain in less than 10 seconds.²² The nicotine concentration in the blood rises rapidly and this phenomenon is known as nicotine boost. The extent of nicotine boost varies between individuals, but the nicotine concentration in the arteries is about twice the concentration in the veins.²³ In the brain, nicotine binds to the nicotinic acetylcholine receptors at the $\alpha_4\beta_2$ subunit.²²

Varenicline

Varenicline is a partial agonist at the $\alpha_4\beta_2$ nicotinic acetylcholine receptor developed specifically for smoking cessation. Varenicline as the tartrate salt has a molecular weight of 361.35 daltons and a molecular formula of $C_{13}H_{13}N_3 \cdot C_4H_6O_6$.⁵ It stimulates dopamine release upon binding to the $\alpha_4\beta_2$ receptor. However, the dopamine release from the ventral tegmental area due to varenicline is less (32 to 45%) when compared to the effect of nicotine.⁵ Thus, cravings and withdrawal symptoms are partially reduced. Another feature of varenicline is the high affinity for the receptor, causing it to remain bound to the receptor for a time. This impedes the ability of nicotine to activate the receptor and thus reduces the satisfaction of smoking a cigarette.⁴

A smoker who is motivated to stop smoking is encouraged to set a date to stop smoking, and varenicline is prescribed one week before the quit date. The initial dose is 0.5 mg daily for the first three days. This is gradually increased to 0.5 mg twice daily for another four days, and then further increased on day 8 to 1 mg twice daily.^{4,6} The recommended treatment is for 12 weeks, although an additional 12 weeks of treatment may be offered to successful patients at the end of the 12 weeks to ensure abstinence.²⁴

Each varenicline tablet is recommended to be taken with food or drink (a glass of water) to reduce nausea. The

gradual titration is also done to reduce the incidence of nausea, which is the commonest side effect. The dose may be lowered temporarily or permanently to 0.5 mg twice daily in patients who cannot tolerate the adverse effects of varenicline. Other reported adverse events are abnormal dreams, insomnia and headache.²⁴ The rare side effects reported were changes in taste, vomiting, abdominal pain, flatulence and constipation. Drowsiness is a listed adverse reaction, thus primary care professionals who prescribe varenicline should warn patients who drive or operate machinery. Most of the side effects of varenicline are mild and can be treated with symptomatic medication.^{24,25}

Use in special populations

Although varenicline is reported to be generally safe, some precaution is required in certain special populations. Varenicline undergoes minimal metabolism and 92% is excreted unchanged in the urine. In the elderly (geriatric) population, a pharmacokinetic study of varenicline demonstrated that it is well tolerated by smokers aged 65 to 75 years. Nevertheless, as elderly patients are more likely to have decreased renal function, renal function should be monitored when prescribing varenicline.

Varenicline may be considered for patients with mild renal impairment.^{6,24} Dosage adjustment is not necessary for patients with mild (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min) to moderate renal impairment (estimated creatinine clearance 30 ml/min). Patients with severe renal impairment (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min) are recommended to start with 0.5 mg daily and titrated as needed to a maximum dose of 0.5 mg twice daily. Patients with end-stage renal disease who are undergoing haemodialysis should be prescribed a maximum of 0.5 mg once daily.²⁵

Thus far, no inhibition of cytochrome P450 enzymes has been reported, and no clinically meaningful drug interactions have been identified. Due to the absence of significant hepatic involvement, varenicline is thus unaffected in those with liver insufficiency. Based on current data, it is recommended that varenicline not be prescribed for smokers younger than 18 years, as the safety and effectiveness of varenicline has not been established in this age group. Similarly, varenicline is not recommended for smokers who are pregnant or breastfeeding, as there are no adequate and well-controlled studies of this group.

Special precaution in patients with mental health problems

The efficacy and safety of varenicline in smokers have been established in randomised, double-blind, placebo-controlled trials.¹⁸⁻²⁰ However, the safety of varenicline in patients with mental health problems is questionable.^{6,26-30} One report found varenicline to be safe for patients with mental health problems and that it was superior in maintaining smoking abstinence. That study was a non-randomised study of 412 smokers in a community clinic that included 111 patients with mental health problems (the primary diagnoses were depression (64), bipolar disorder (14), psychosis (7), psychosis and depression (24) and eating disorder (2)). However, no firm conclusion can be drawn, as the sample size of the study was small and the study included varying psychiatric diagnoses.⁶ On the other hand, the literature has also reported several cases of neuropsychiatric symptoms such as suicidal ideation, suicidal behaviour, erratic behaviour and drowsiness as a result of varenicline use.³¹ There have also been reports of activated psychotic relapse in schizophrenia, hypomania with agitation in a bipolar II disorder, and induction of a manic episode in a bipolar patient.^{26,32} Also published was a case of a person who shot his neighbour while in a state of delirium caused by taking varenicline with a high dose of alcohol, though it was unclear whether the episode was related to the drug or to a state of alcoholic intoxication. Other post-marketing reports included agitation and depression.³³ Most recently, acute hepatic injury with raised liver enzymes was reported in an alcoholic patient. The level of the alkaline phosphatase enzyme was reported to reduce to normal within one month of discontinuation of varenicline, and the level of the enzyme aminotransferase was shown to reduce to normal after four months of discontinuation of the drug.

In all the examples stated above, it was not clear whether the psychiatric symptoms were related to the drug or to nicotine withdrawal symptoms, and a causal connection or lack of connection between varenicline and these symptoms was not established.²⁴ However, the Diagnostic and Statistical Manual of Mental Disorders (4th edition) has acknowledged that the psychological symptoms of nicotine withdrawal include insomnia, irritability, frustration or anger, anxiety, difficulty concentrating, restlessness, and a dysphoric and depressed mood.³⁴ Varenicline is also reported to cause dysregulation of the dopaminergic system, and this may lead to the exacerbation of psychotic symptoms in patients with psychotic disease. Varenicline has also been linked to neuronal $\alpha 7$ nAChR1, which is linked to major psychiatric disorders.^{26,32}

Thus, when prescribing varenicline to mental health patients, primary care doctors need to consider the beneficial and adverse effects of varenicline. Prior to prescribing varenicline, it is thus important to establish the presence of mental health problems. Based on current information and on the knowledge from the literature, it is recommended that: (1) Patients with mental health problems, their families and carers should be given advice and alerted to the risk of varenicline in relation to their existing mental illness. (2) Alternative pharmacotherapy should be considered for smokers with mental health problems who wish to stop smoking, as thus far there is insufficient data to certify the safety of varenicline for this population. (3) For smokers with mental health problems who choose to take varenicline, advice should be given to their families and carers to be alert to changes in mood and behaviour. Patients who develop agitation, hostility, depressed mood or suicidal thoughts should be advised to stop taking varenicline and contact their doctor immediately.

Comparing the effectiveness and safety of varenicline with other available treatments for smoking cessation

A study of smokers in a primary care setting reported that 54.6% of smokers treated with varenicline were abstinent at 12 weeks compared to those on placebo (11.6%). At 52 weeks, smokers on varenicline (22.4%) were still superior in their abstinence to the placebo group (3.9%).²⁴ A meta-analysis report also showed that varenicline tripled the success rate compared to a placebo, and that it was more effective than other medications used singly.⁵ Varenicline was also reported to be superior to nicotine patches in producing continuous abstinence rates by week 4 and at one year after stopping smoking.³⁵ A recent report that evaluated the cost-effectiveness of varenicline and nicotine replacement therapy (NRT) for smoking cessation in four European countries (Belgium, France, Sweden and the UK) also found varenicline to be superior to NRT. This study compared smoking-related morbidity and mortality and the quality of the adjusted life-years gained and found varenicline to be more cost-effective than NRT.³⁶ Varenicline was also found to be more cost-effective and cost-saving compared to other smoking cessation treatments such as bupropion and nortriptyline.⁴

Varenicline in the family practice setting

Varenicline has been used widely in primary care settings in developed countries.^{4,6,24,25,37} It was licensed for use in the USA in May 2006 and in Europe in September 2006.

Varenicline is also now prescribed in primary care settings in the UK under the National Health Service.^{6,37} However, despite offering a new option for smoking cessation, the latest literature reports have raised numerous issues pertaining to varenicline.^{24,25} Besides medication, primary care doctors should also take account of the importance of motivating the patient to stop smoking and that the success of drug treatment is dependent on its combination with behavioural intervention.

Promoting smoking cessation is an achievable task and is not time consuming. Brief interventions, which include simple inquiry (ask, advise, assess, assist and arrange to stop smoking), take less than three minutes to perform and should be offered to all smokers.⁴ Unfortunately most doctors and health professionals in the primary care settings are not trained formally in smoking cessation and some have misconceptions about how best to help a smoker stop smoking and what should constitute a smoking cessation programme. There is, thus, a need for formal training for health professionals interested in offering smoking cessation services to primary care patients.

Conclusion

Cigarette smoking continues to be an important cause of morbidity and mortality worldwide. Effective smoking cessation treatment is thus needed to curb this public health problem. Due to its unique partial agonist property, varenicline – a new class of drug for smoking cessation – is a valuable addition to the existing pharmacological agents for smoking cessation. In general, varenicline has the potential to be highly effective in promoting and maintaining smoking abstinence, although its safety in smokers with mental health problems needs to be established further.

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